Sensitivity to Biases of Case-Control Studies on Medical Procedures, Particularly Surgery and Blood Transfusion, and Risk of Creutzfeldt-Jakob Disease

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Key Words

Creutzfeldt-Jakob disease · Epidemiological studies · Etiology · Latency analysis

Abstract

Background: Evidence of risk of Creutzfeldt-Jakob disease (CJD) associated with medical procedures, including surgery and blood transfusion, is limited by susceptibility to bias in epidemiological studies. **Methods:** Sensitivity to bias was explored using a central-birth-cohort model using data from 18 case-control studies obtained after a review of 494 reports on medical procedures and risk of CJD, systematic for the period January 1, 1989 to December 31, 2011. **Results:** The validity of the findings in these studies may have been undermined by: recall; control selection; exposure assess-

ment in life-time periods of different duration, out of time-at-risk of effect, or asymmetry in case/control data; and confounding by concomitant blood transfusion at the time of surgery. For sporadic CJD (sCJD), a history of surgery or blood transfusion was associated with risk in some, but not all, recent studies at a ≥ 10 year lag time, when controls were longitudinally sampled. Space-time aggregation of surgical events was not seen. Surgery at early clinical onset might be overrepresented among cases. Neither surgical history nor blood transfusion unlabelled for donor status, dental treatments or endoscopic examinations were linked to variant CJD (vCJD). **Conclusions:** These results indicate the need for further research. Common challenges within these studies include access to and content of past medical/dental treatment records for diseases with long incubation periods.

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Introduction

Creutzfeldt-Jakob disease (CJD) is a neurodegenerative disorder with deposition of a pathological isoform (termed PrP^{Sc}) of the normal cellular prion protein (PrP^C). CJD exists in three forms: sporadic (sCJD), which is acquired, either variant (vCJD) or iatrogenic (iCJD) CJD, and cases caused by mutations in the gene-encoding PrP^C, here denoted for purposes of simplicity as genetic CJD (gCJD) [1]. The etiology of vCJD has been linked to dietary exposure to bovine spongiform encephalopathy (BSE) or transfusion of blood from infected donors [2, 3]. The cause of sCJD is unknown.

Etiological epidemiological research on vCJD and sCJD related to secondary transmission in the medical settings has been limited. Analytical studies in the UK, encompassing the majority of the reported cases of vCJD, have not indicated an increased risk from surgical or dental procedures [4, 5]. Studies on medical procedures as a risk factor for sCJD are compromised by methodological limitations [6, 7]. Results of recent studies on surgical history introducing methodological improvements such as latency analysis, etiological classification of surgical procedures (SP) and SP data obtained from national registries (and, therefore, theoretically independent from recall bias) [8–10], have raised new hypotheses, although space-time relationships between procedures have not been observed [11].

The ultimate goal of this review is to ascertain the scientific basis for specific public health recommendations when drafting EU-wide guidance for the prevention of sCJD transmission in medical settings (ECDC project 1250) [12]. To achieve this, an attempt was made to identify a susceptibility to bias and evidence of risk of CJD associated with medical procedures, including surgery and blood transfusion (BT), in epidemiological studies.

Methods

In order to identify documents reported from 1989 onwards in English, searches were done using MEDLINE and EMBASE with similar strategies for the period January 1, 1989 to December 31, 2011. First, we adopted a general strategy based on MEDLINE MeSH terms 'prion diseases' OR 'prions' OR 'Creutzfeldt-Jakob syndrome' AND 'case-control studies' OR 'cohort study' or TEXTWORDS 'Creutzfeldt-Jakob', 'case-control' or 'cohort'. Second, findings were added after the EMBASE search, which included Emtree thesaurus analogous to the above-mentioned MeSH terms, i.e. 'cohort analysis'. Search terms for specific medical procedures or blood-related treatments were not used at this level. After the elimination of dupli-

cates, searches provided 506 documents as primary results shown in figure 1. Of these, 34 fulfilled the following two inclusion criteria indicated by quotation marks: mention in the title or abstract of either 'blood transfusion (BT)', blood derivatives, blood components, plasma products' or 'diagnostic or therapeutic invasive major and minor medical procedures, endoscopic procedures, ophthalmological procedures, procedures associated with allogeneic tissue implants (dura mater, tendon, etc.)' when applied by at least one of the two reviewers, J.P.C. and M.R.T. The use of exclusion criteria such as letters, reviews, metaanalyses, theoretical issues, methodological papers and documents without abstracts, by a concordant decision by two independent reviewers applying consensus criteria after full document perusal, resulted in the elimination of 6 documents. In order to improve completeness, 5 research reports, 3 of which were published before 1990, and 2 recent papers on BT and surgical history were added [13–17]. Thirty-three documents pertaining to case-control studies and several studied cohorts [4–10, 13–38] were examined in full text. Thirteen were excluded from the systematic review since: (a) they focused on biographic residential space-time relationships [19]; (b) they were methodological [6–8, 20]; (c) they focused on the follow-up of national single cohorts of persons exposed to treatment with human pituitary growth hormones in the UK, The Netherlands and the USA [18, 21–24], or with BT or plasma products without data on nonexposed persons [37, 38], or (d) they related to human dura mater graft recipients [25]. The search on reports up to 2011 provided 20 full-text documents on 18 case-control studies on CJD where BT or medical procedures were mentioned as potential exposures in the Methods or Results, either as the primary subject of study or as one of a number of potential risk factors, e.g. genetic, occupational or dietary [4, 5, 9, 10, 13–17, 26–36] (see fig. 1 for details of the selection flow).

The remaining 20 papers related to 18 case-control studies on either sCJD, vCJD or both conditions, and addressed etiological hypotheses including SP and/or BT or history of exposure to plasma products. Some studies generated more than one publication [9, 10, 27, 28]. When studies included additional cases or controls the second study was selected for analysis [15, 26]. We extracted data from Methods and Results, relevant to the study of medical procedures and blood or plasma products, as risk factors in the 18 studies, and we then summarized them.

Sensitivity to biases in the study design for hypotheses related to medical procedures was explored using the study central birth cohort model as proposed by Rothman et al. [39] and Wacholder [40], which was interpreted from a graph, and assessed basic rules of epidemiological analysis, e.g. symmetric exposure assessment, the potential impact of recall or the control of confounding. Medical procedures encompass different interventions such as SP, endoscopies with or without biopsy, dental treatment, transfusion of blood components, or the use of plasma products, all of which involve single exposures. Less frequently there were extended exposures such as coagulation factors in the treatment of hemophilia. In this study the sources of biases that were assessed related mainly to discontinuous exposures and included: (1) type of controls; (2) temporal relationships between case-incidence periods and sampling periods for controls; (3) the source of information on exposures; (4) lifetime references for exposure measurement and individual classification by exposure, and (5) space-time re-

Fig. 1. Flow diagram of the study selection process.

lationship of exposures. The grading of scientific evidence and the application of quality criteria [41, 42] in order to support recommendations in public health, based on this paper and other literature reviews, will be reported separately.

Results

Study Purposes and Domains

The 20 papers assessed in this report included 1 on CJD (all forms included) [30], 3 on vCJD [4, 5, 33], 17 on sCJD [9, 10, 13–17, 26–29, 31–36] and 1 on gCJD [16]. Seventeen reports focused on surgical history [4, 9, 10, 13–16, 27–36] and 14 also included data on BT [4, 13–16, 27–32, 34–36]. Two UK studies addressed BT only [17, 26]. Dental treatment was addressed in 12 reports [4, 5, 10, 13, 14, 27, 28, 31, 32, 34–36], and endoscopic procedures in 3 [9, 28, 36]. Other procedures such as tonometry or electro-

myography were rarely studied. All the studies were carried out in industrial countries. One was conducted in Australia [31], 3 in Japan [13, 30, 35], 9 in a European country (Germany, Italy, Switzerland and the UK, including vCJD) [4, 5, 14, 16, 17, 26, 29, 34, 36], and several in two or more European countries [9, 10, 27, 28, 32].

The studies chronologically defined by case recruitment and control sampling are shown in figure 2. Case recruitment in a minority of the studies was before the 1990s but in most it was after 1990, with the study by Esmonde et al. [26] including cases from two separate study periods. In general, earlier studies involved case series and later studies were based on national registries for CJD, which had been established following the identification of BSE in the UK in the late 1980s. Studies based in a single country or in countries with small populations require extended periods for data accrual. Studies from Australia, Italy, Japan and Denmark/Sweden include data

Fig. 2. Outline of study periods defined by the clinical onset of CJD cases and schematic representation, longitudinal or end of study, of the sampling format of controls. Study period symbols underline first-author labels (color online version only).

from extended study periods as defined by the clinical onset of cases [9, 10, 16, 31, 35]. The studies by countries included in the EuroCJD consortium were carried out over shorter periods, and included different types of controls [27, 28, 32].

Methodological Aspects

Methodological details of the 18 case-control studies are summarized in figure 2 and table 1. In general, multiple hypotheses were examined by the EuroCJD consortium, the Australian and the Swiss studies [27, 28, 31, 32, 36]. Investigators used a questionnaire formulated by the EuroCJD group [5, 32], which included questions on diet, contact with animals and occupation, both for sCJD [27, 28, 31, 32, 36] and vCJD [4]. A few studies focused on specific hypotheses for sCJD such as BT [16, 17, 26], surgical events (taken as life stressors) prior to onset [29] and ophthalmological surgery, sometimes including sCJD and vCJD in the UK [33] or dental treatments in the UK for vCJD [5]. Recently, studies by the EurosurgCJD group

were conducted using data on the national populations of Denmark/Sweden. Studies from Italy, Japan, Switzerland and the UK focused on risks related to prior medical history, mainly for medical and SP [4, 9, 10, 16, 34–36], some of which included BT [4, 16, 17, 34–36].

In general, controls recruited from hospitals or medical establishments (denoted in this paper as hospital controls) were scarcely used after 1998. Studies from Italy, Japan and the UK used non-CJD cases accrued from CJD surveillance notifications as controls [16, 17, 33, 35]. A UK study, which focused on dental surgery, and a Swiss study used a mix of hospital and population controls [5, 36]. Hospital or primary care-generated controls or a mixed group of hospital and neighborhood controls were included in 11 studies [5, 14–16, 26–30, 33, 35], and population control sets in 6 studies [4, 9, 10, 13, 31, 32, 34], with 3 sets randomly selected from the study population [4, 9, 10, 34]. In general, when details are provided, two patterns emerge (fig. 2). Hospital controls, either from hospitals or reported non-CJD cases, matched or not, were longitudinally

Fig. 3. Graphical representation of selected results. m = Months; y = years; o. = onset; b.o. = before onset; adj. = adjusted.

Table 1. Methodological features of case-control studies testing associations of medical procedures/surgery/blood with CJD

Authors	Study purpose (outcome, tested hypotheses)	Study base and study period	Cases n	Type of controls	Matching variables
Kondo et al., 1982 [13]	sCJD Life history Animal contacts Medical, surgical and dental history BT	Japan 1975–1977	60 (37 definite, 23 probable)	56 neighbors 47 spouses	Age 5 years, sex
Davanipour et al., 1985 [14]	sCJD Dietary factors Medical history Surgery Blood Endodontic procedures	Pennsylvania, USA and other mid-Atlantic states	26 (20 definite, 6 probable)	40 18 relatives 22 hospital patients	Age 5 years, sex
Harries-Jones et al., 1988 [15]	sCJD Blood Medical history Diet, smoking Animal contact Family history of dementia	England and Wales 1980–1984	122 (93 definite, 29 probable)	2 per case (184) Hospital patients (1 neurological, 1 medical)	Age 4 years, sex, hospital
Esmonde et al., 1993 [26]	BT	England and Wales 1980–1984 and UK CJD surveillance 1990–1992	total 155 cases (92 definite, 63 definite or probable) out of 202 recruited	184 (see above) plus 63 hospital controls total 247 hospital controls	Age and sex
Van Duijn et al., 1998 [27]; Zerr et al., 2000 [28]	sCJD Genetic factors Lifetime medical history Blood, dental Occupational Animal exposures Diet	6 European countries 1993–1995	405 (199 definite and 206 probable)	405 hospital patients	Age 5 years, sex, hospital
Collins et al., 1999 [31]	sCJD Medical history Blood, dental Others selected: Occupational, Residential	Australia 1970–1997 registered	241 (151 definite and 90 probable)	784 population random telephone dialing	Age 5 years, sex, place of residence
Laske et al., 1999 [29]	sCJD Stressful life events: Psychosocial stress, Surgery in hospitals, Medical examinations	Germany 1997–1998 surveillance	37 sCJD (7 definite and 30 probable)	37 hospital patients without dementia (stroke, dizziness, etc.)	Group-matched by age and sex
Nakamura et al., 2000 [25]	CJD Dura mater grafting Surgery BT Occupation	Japan 1996–1999 surveillance	52 out of 83 CJD reported cases	102 hospital patients, with ‘injuries and diseases not related to prion’	Age 2 years, sex, hospital
Ward et al., 2002 [32]	sCJD Lifetime surgical history BT	4 European countries 1993–1995	326 (169 definite, 157 probable)	326 population random telephone dialing in 2000	5-year age group and sex matching, country

Table 1 (continued)

Control sampling design	Source of information on exposure	Strategies for control for lifetime, person-year, exposure bias	Strategies introduced to control confounding, avoiding recall or improving measurement or quality of lifetime medical history	Specific analysis of medical procedures in cases and controls	
				latency analysis?	space-time analysis of exposures on study?
Not explicit Likely absent	Cases = proxy phone interview Controls = direct phone interview	Not mentioned	Controls were reasonably healthy individuals	Operations up to onset 5 and 10 years before onset	Not reported
Not explicit Likely absent	Cases = proxy phone interview Controls = direct phone interview	Not mentioned	Mail questionnaire before interview; same questions formulated in different ways	Birth to 14 years 15 years to 3 years before onset	Not reported
Longitudinal	Cases = proxy interview Controls = proxy interview	Cases = time to clinical onset Controls = time to current hospital admission	No defined latency No strategies Lifetime medical, and surgical history	Not reported	Not reported
Longitudinal	Cases = proxy interview Controls = proxy interview	Cases = time to clinical onset Controls = time to current hospital admission	No defined latency No strategies Lifetime; all past medical events related to current admission in controls excluded	Not reported	Not reported
Longitudinal	Cases = proxy interview Controls = proxy interview (when possible)	Matching	Not mentioned	Lag-time >2, >4 and >10 years	Not reported
End of study	Cases = medical record on site examination Controls = direct phone interview by a company	By 5-year age group matching	Not mentioned	Not reported	Not reported
Longitudinal	Cases = interviewers Controls = interviewers (both to proxy, close relatives)	Matching mean age cases 66 years, controls 65 years	Pretest sample examined using medical records	Last 6 months Up to 8 years before onset Lifetime	Not reported
Longitudinal	Cases = physicians Controls = physicians	Matching Mean age cases 63.7 years, controls 62.5 years	Examination of medical records	Not reported	Not reported
Post (5–8 years earlier for cases) end of study	Cases = proxy interview (spouse) Controls = direct computer-assisted phone interview	By 5-year age group matching	Not mentioned	Not reported	Not reported

Table 1 (continued)

Authors	Study purpose (outcome, tested hypotheses)	Study base and study period	Cases n	Type of controls	Matching variables
S-Juan et al., 2004 [33]	sCJD vCJD Past ophthalmic (intraocular, extraocular) surgery; year, hospital, type Space/time links	UK surveillance unit 1990–2002	Definite and probable sCJD 510 vCJD 125	226 hospital patients 106 population for sCJD 67 hospital patients 155 population for vCJD	Age- and sex-matched
Everington et al., 2006 [5]	vCJD 6 categories of dental treatment from 1980 onwards	UK surveillance unit	Definite and probable 130 cases out of 159 reported up to December 2003	Mixed, 149 community up to 4/1 53 hospital controls for 66 vs. 53 cases not neurological diagnoses	Age (± 4 years)- and sex-matched
Ward et al., 2006 [4]	vCJD Dietary, medical, surgical, dental, BT, invasive, occupational, contacts with animals/pesticides	UK surveillance unit	Definite and probable vCJD 136 reported 1995–2003 Median age at onset 26 years	922 random age-weighted population sample >5 years resident in UK with 1 resident alive relative median age 33 years	None
Ward et al., 2008 [11]	sCJD Medical procedures, mainly surgical Space/time relations	UK surveillance unit	431 (298 definite, 133 probable) Median age 51 years 267 subgroup	454 random sample population Median age 67 years	None
Hamaguchi et al., 2009 [35]	sCJD Lifetime medical and surgical history Blood	Japanese resident	753 definite or probable, 1999–2008 Mean age 67.7 years	210 reported surveillance controls Mean age 59 years	None
Ruegger et al., 2009 [36]	sCJD Lifetime medical history Drug use Occupation Diet	Swiss resident population at high sCJD incidence period	69 cases 61 definite 8 probable Onset at 2001–2004	224 controls 69 GP based 2004–2005 (see exclusion criteria) 155 random telephone dialing, 2005	Age, sex District and GP list Age, sex, residence by language
Mahillo et al., 2008 [9]; De Pedro-Cuesta et al. 2011 [10]	sCJD Surgical and endoscopic history	Danish and Swedish resident populations	167 113 definite 54 probable	Population, 835 random, matched for age, sex, country 2,224 random	Age, sex, residence None
Puopolo et al., 2011 [16]	sCJD gCJD Lifetime history of BT and surgery	Italy surveillance period 1993–2008	741 sCJD (563 definite) Mean age 67 years 175 gCJD Mean age 58 years	482 reported surveillance controls Mean age 61 years	None
Molesworth et al., 2011 [17]	sCJD Lifetime history of BT	UK surveillance period May 1, 1990 to Dec. 31, 2010	1,206 sCJD (978 studied) Age not reported	585 reported surveillance controls (136 studied) Age not reported	None

Table 1 (continued)

Control sampling design	Source of information on exposure	Strategies for control for lifetime, person-year, exposure bias	Strategies introduced to control confounding, avoiding recall or improving measurement or quality of lifetime medical history	Specific analysis of medical procedures in cases and controls	
				latency analysis?	space-time analysis of exposures on study?
226 (1990–1998) 1/1 hospital 106 (1999–2002) 1/1 population 67 (1996–2002) 1/1 hospital 155 (since 1998) up to 4/1 community	Relatives, general practitioners records, case notes, records, case files in cases and controls	In cases intervals pre- (number of years) and post-clinical onset	Not mentioned	Not mentioned Graph on latency between last eye surgery and onset for cases	Operation year and hospital in cases
Sampling: same GP practices and same hospital as cases for community and clinical controls	Interviews to relatives using standardized questionnaires Categories by review by dental practitioner	Not mentioned	Not mentioned	Not reported	Not reported
Post-code sectors, in part selected clusters matched to vCJD cases 2002–2003 End of study	Relatives Cases = nurse surveillance questionnaire Controls = National Centre interviewers, questionnaire	Proportions exposed Controls adjusted to cases Birth cohort distribution	Adjustment by birth cohort, sex, residence	Not reported	Not reported
Post-code sectors, in part selected clusters matched to vCJD cases 2002–2003	Cases = nurse interview to relatives Controls = National Centre interview to relative	Analysis stratified by decade of birth	Complementary subgroup analysis (267 cases onset 2001–2005, controls interview 2002–2003) Space/temporal analysis	Subgroup analysis of 10 -year periods up to ≥20 years before onset Analysis adjusted for previous surgery, birth cohort and region	Surgery in cases
Longitudinal, by notification time	CJD surveillance and clinical records	Stratified analysis by age at onset	Direct perusal of medical records	Not reported	Not reported
End of study period	EUROCD questionnaire Proxy interviews, response rate 68%	Not mentioned	GP controls noncompliant or with severe disease or were excluded Exposures before and after 1980	Not reported	Not reported
Longitudinal, selection from retrospective registered resident population	Operating surgeon or acting physician at hospital	Strict control by index and hospital discharge dates; uncontrolled ambulatory procedures	Validated residential history in Sweden Lack of blood transfusion data Use of an etiological classification of surgical procedures	>1 year, 1–9 years, 10–19 years, ≥20 years (alternatively 1–14 years and ≥15 years) before onset/index date	Hospital and date analysis of surgical discharges of cases ≥20 years before onset
Longitudinal as reported to surveillance in 1993–2008	Cases = at notification by phone interview or visit to treating physician. Controls = same procedures and timing	Differences in lifetime at onset for cases and controls were assessed	Confounding of blood by surgical history controlled at data analysis Recall effect assessed from differences in findings for sCDJ and gCJD	Yes, for exposure at >10-year lag	No space-time analysis
Longitudinal as reported to surveillance during same period	Cases = data obtained from surveillance records Controls = same source	Lifetime at risk of exposure measured, not reported	Models adjusted for surgical history, age at onset, notification year	Yes, for exposure at >10-year lag	No space-time analysis

Table 2. Methodological classification of case-control studies by type of controls, consistency and type of measurement assessing exposure status, and (far right column) number (1–4) and type (I–V) of items potentially determining vulnerability to bias

Type of control, hospital vs. population (I)	Matching by age/sex (II)	Predominantly type of controls sampling: longitudinal or mid-point vs. end of study (III)	Symmetric source of exposure assessment (IV)	Adjustment method for time at risk of exposure determining exposure status (V)	Number (n) and type of items potentially determining (alone or in combination) sensitivity to bias (confounding not excluded) present in study design			
Hospital (purely hospital patients or mixed, in part hospital controls)	Yes	Longitudinal or mid-point	Yes	Harris-Jones et al. [15] ^a	(1) I			
				Esmonde et al. [26] ^a	(1) I			
				Laske et al. [29] ^a	(1) I			
				Van Duijn et al. [27] ^a	(1) I			
				Zerr et al. [28] ^a	(1) I			
				Nakamura et al. [25] ^a	(1) I			
				S-Juan et al. [33] ^a	(1) I			
				Everington et al. [5] ^a	(1) I			
	No	End of study	Yes	Ruegger et al. [36] ^a	(2) I, III			
				No	Davanipour et al. [14] ^b	(4) I, III, IV, V		
				No	Yes	Hamaguchi et al. [35] ^c	(1) I	
						Puopolo et al. [16] ^d	(2) I, V	
Molesworth et al. [17]	(1) I							
No	End of study	Yes	No					
			No					
			Population (neighborhood, relatives, resident population sample)	Yes	Longitudinal or mid-point	Yes	Mahillo et al. [9] ^{a, e} , 2008	–
							de Pedro-Cuesta et al. [10], 2011	
Kondo et al. [13] ^a	(1) IV							
No								
No	End of study	Yes		Collins et al. [13] ^a	(2) III, IV			
				Ward et al. [32] ^a , 2002	(2) III, IV			
				No	Longitudinal or mid-point	Yes	Mahillo et al. [9] ^e , 2008	
							Ward et al. [4] ^f , 2006	
Ward et al. [11] ^f , 2008								
No								
No	End of study	Yes	No					
			No					

^a By matching for age; ^b none; ^c analysis stratified for age at onset; ^d assessed impact of a 6-year difference in mean age at onset in OR = 5; ^e analysis of equal lifetime intervals by time-windows design; ^f by adjusting for birth cohort in the analysis.

sampled [5, 16, 17, 27, 28, 33, 35, 36]. Population controls were sampled at the end [4, 31] of the interval for case inclusion [32], except in EurosurveillanceCJD [9, 10] which, using annual counts of population registries, mimicked longitudinal procedures used in studies with hospital controls.

There was considerable variation in the type of medical procedures assessed. The EuroCJD questionnaire, administered either by direct or telephone interview, was used in approximately half of the studies and produced a standardized list of reported procedures. An inconsistent, i.e. asymmetrical, collection of surgical or BT histories was suggested or evident from descriptions in some studies in which, for example, the controls were the direct

informants about their own history [13, 14, 31, 32]. In CJD cases it is rare for the patient to be able to provide any data and this is usually derived from an interview with family members. The time point of data collection was described in only a few studies.

The use of a classification system for diagnoses and procedures was not mentioned except for SP in EurosurveillanceCJD in which an etiological classification of SP was added to the anatomical one traditionally used in Nordic countries [9, 10]. In reporting an analysis of BT, studies did not mention the differential recording of whole blood, labile components, type of cells or type or number of units. All studies used data on medical history obtained from personal in-

Fig. 4. a Demographic background of a case-control study conducted at end of the 20th century. Ad hoc modified Lexis diagram of the central birth cohort.

interviews, or in some recent studies [4, 16, 34, 35] a retrospective review of hospital and/or general practitioner medical records. Data from national hospital discharge registries with diagnoses and medical procedures coded by specialists at discharge were used in EuroSurgCJD [9, 10].

The time reference for exposure assignment in cases, which was often not explicitly stated, encompassed life-long surgical or BT history up to clinical onset [16, 33, 35], up to 1 year prior to onset [9, 10] or up to 3 years prior to onset [28]. Less frequently, authors focused on the period preceding the disease onset and examined surgery during the 2 years prior to onset [28] or during a longer period as in the case of a stressful event in a small German study [29]. A British study of ophthalmic surgery and a Japanese study of surgery in general investigated surgery following disease onset as a putative source of instrument contamination [33, 35]. The at-risk periods for exposures in the controls were often not explicit, but some studies mentioned lifetime up to interview [16, 32, 35] or lifetime intervals purposely defined by index dates [9, 10].

Consideration of latency or lag periods of different durations from exposure to the onset for risk analysis in sCJD were incorporated in early studies [13, 14], the first

EuroCJD study [28], EuroSurgCJD [9, 10] and recent British and Italian studies [16, 17, 34]. Surgery or medical procedures before or after 1980, a time point related to BSE exposure as a potential etiological factor, were included as a variable in some studies [4, 28, 36].

Table 2 lists the studies according to the category of exposure assessment in the controls and indicates the types of control groups, the use of age and sex matching, the timing of the interviews in the controls in relation to the cases and whether or not there was symmetric assessment of exposures, i.e. whether information from the controls was obtained directly or indirectly from a family member. Nine reports, the largest group, used hospital, age- and sex-matched controls and consistent exposure assessment. There is a trend in recent studies to include population controls only [4, 9, 32, 34], longitudinal or midpoint sampling [9, 16, 17, 32, 34] and consistent exposure assessment [4, 9, 10, 16, 17, 34].

Findings

Results for medical procedures, including surgery, BT, endoscopies and dental treatments are described in the online supplementary table (for all online suppl. material,

Fig. 4. b Outline of lifetime course and history of medical procedures and CJD diagnoses of a cohort whose members are represented if born during the period 1920–1940. Data for persons pertaining to peripheral birth cohort components are shown only in part (CJD diagnoses, medical procedures). Symbols represent potential time references, CJD diagnoses and time point-related undergone medical procedures. The thin black continuous lines depict the lifetime course, i.e. age in years for persons in the central part of the cohort. The thin black discontinuous bands represent age strata and the parallel thick band at 90 years indicates a hypothetical end of birth cohort follow-up. The graph also describes a

follow-up in 2000, at ages ranging from 60 to 80 years for the individuals of the central birth cohort, with events that occurred after this date also indicated. CJD diagnoses are depicted if clinical onsets occurred during the period 1981–2000, i.e. incidence study period. The red discontinuous lines limit the study incidence period and the thin blue discontinuous ones indicate the latency bands, enabling the individually adjusted latency time to be calculated (color online version only). The red discontinuous lines limit time units of the study incidence period and potential controls' sampling intervals.

see www.karger.com/doi10.1159/000339318) and figure 3. Data for CJD (all forms included), gCJD and vCJD were sparse [4, 5, 16, 30]. Exposure to human dura mater grafts was significantly associated with CJD, odds ratio (OR) = 32 [30]. In 155 cases of gCJD, no risk excess was seen for either BT or surgery at >10-year or no lag [16]. In the UK studies of vCJD no association was reported for lifetime surgery except for minor SP and dental extractions, both of which had a wide 95%CI [4, 5]. The proportion of cases and controls with positive BT history, unlabeled for donor status and adjusted by birth cohort (not shown in fig. 3), was similar in both groups [4]. Results for sCJD are summarized as listed below.

Surgery and, when Specified, Invasive Dental Treatments

With regard to lifetime surgical history, 7 studies with clinical or mixed controls reported no statistically significant associations [29, 33, 35] or statistically significant protective associations [15, 27, 28, 36]. Four studies using community or mixed controls [31, 32, 34, 36] and 1 with hospital controls [16] reported moderately significant associations with lifetime surgical history, OR range 1.6–2.0. The significant association with no lag persisted at >10-year lag [16]. Nonsignificant associations at >1-year lag from onset became higher and significant at ≥20-year lag in a register-based study [9, 10]. In the only study

Fig. 4. c Lifetime course and history of medical procedures of a number of individuals (cases, controls, and persons not included in study) selected from the birth cohort corresponding in theory to a case-control study of sCJD with the first cases born in 1920 and the last in 1940 with onsets in the period 1981–2000. Symbols represent potential time references, outcomes and exposures, biologically relevant for specific individuals assuming an incubation period ≥ 20 years. The thin black continuous lines and the thin blue discontinuous lines represent the time references described in **b**. The red discontinuous lines limit time units of the study incidence period and potential controls' sampling intervals.

attempting to control confounding, an OR = 1.45 at >10 -year lag for history of surgery became nonsignificant when adjusted for BT at the same time lag [16].

Findings for surgery at specific anatomic sites or settings provided varied results. Few studies had positive findings at no lag: (1) a statistically significant higher frequency of surgery up to 10 years preceding clinical onset was found in EurosurgeCJD, mainly in coronary surgery and after hospital admission in a German study [9, 29]; (2) when using an etiological classification, the only positive association in the EurosurgeCJD study was seen with retinal surgery, which had a mean latency of 9 years to clinical onset [9, 10]; (3) associations were seen for orthopedic, gastrointestinal and gynecological procedures in studies using community [31, 32] or mixed [36] controls, and (4) significant, protective but moderate associations were seen with surgery of the spine in a study

using hospital controls [32, 36] and with tonsillectomy [32] and appendectomy [32, 36] in studies using population and hospital controls, respectively.

At different time lags significant findings varied. A history of surgery of the face, head or neck from the age of 15 years to 3 years before onset was a risk factor for sCJD in an early study in the USA using 'neighbourhood healthy' or a set of clinical and population controls [14]. In EurosurgeCJD, associations were seen for several body system categories of SP with ≥ 20 -year lag and when using an etiological SP classification, at a latency of 10–19 years for surgery of peripheral nerves and in which skeletal muscle was contacted [9, 10].

Studies on surgery or medical procedures performed immediately preceding or after clinical onset suggest an excess of ophthalmological [33, 35], neurosurgical [35] and other SP [29, 35].

Only 1 of 7 studies of sCJD and dentistry [13, 14, 27, 28, 31, 32, 36] reported a significant positive association with dental treatment, namely for invasive procedures before 1980 [36].

The search for space-time clustering of surgical interventions was investigated for sCJD cases in some studies with positive results [9, 34], but failed to provide evidence of any links. Similar attempts for controls were not mentioned.

Blood and Blood Products

Findings for a lifetime history of BT in relation to the risk of sCJD were reported in 11 studies. At no lag, protective ($OR < 1$) effects clearly predominated, being modest but statistically significant in 2, the first EuroCJD and the Swiss studies [27, 28, 36], and nonsignificant in 6 studies [13–15, 26, 32, 36]. Other nonsignificant studies include 1 with unreported OR magnitude [35] and 2 British and Italian studies [16, 34]. An increased risk from BT was found in the only study assessing BT at ≥ 10 -year lag time from onset, which identified statistically significant $OR = 4.09$ and $OR = 5.01$, crude and after adjustment for genotype and surgical history, respectively [16]. These findings were not replicated in another study using a similar methodology [17].

Invasive Diagnostic Procedures

A protective effect for gastrocolonoscopy was seen in Switzerland, using primary care controls [36]. However, no association was seen either using age-matched clinical controls in the first EuroCJD study [27, 28] or after adjusting for surgery in EurosurveillanceCJD [9].

Discussion

This review shows that there have been three main risk-based approaches to a potential relationship between medical procedures and CJD, i.e. the case-control design, time-space analysis and cohort studies of persons exposed to recognized iatrogenic factors. The results of these studies are inconsistent and there is no convincing overall evidence that specific medical or SP are associated with an increased risk of developing CJD other than the use of human dura mater grafts. However, all the studies, except perhaps for EurosurveillanceCJD, have methodological problems that may compromise any definitive conclusions [7], and the body of epidemiological evidence cannot exclude the possibility that surgery or BT may be rarely associated with risk of CJD.

Understanding susceptibility to bias and how this influences the interpretation of results requires a multifaceted approach.

Design

The study design improved rapidly after vCJD was described and, in many studies since 1998, source populations were identified after national surveillance programs for CJD were officially established. All the studies except EurosurveillanceCJD [9, 10] correspond to the cumulative case-control type and address risks such as surgery, which have been defined before control selection begins, i.e. after the potential cases have been identified with the controls selected from noncases [39]. Potentially introduced biases are multiple since (a) a case-control study has been described as ‘a cohort study with data missing at random and by design’ [40], (b) most studies address lifetime risks and (c) the majority of cases studied in this review were aged 60–79 years at onset during the period 1990–2008 and represent the 1920–1940 birth cohort (figs. 4a, 4b).

Diagnosis and Case Selection. Bias related to case selection, e.g. related to CJD misdiagnosis, is unlikely except in earlier studies in which only a proportion of all cases may have been included [13, 14]. Overall national mortality rates for sCJD are similar in many countries in which these studies have been carried out and the rates appear to be largely independent of postmortem rates in suspected cases. This suggests that case ascertainment for sCJD has been relatively uniform in many countries in which these studies have been carried out [43]. The impact of potential false-positive diagnoses, such as Alzheimer’s disease or Lewy body disease, among cases without pathological confirmation of the diagnosis is unlikely to be an important confounder [44, 45].

Control Selection. Some authors have attributed evidence of a protective effect from some medical or SP to be a result of bias related to the use of hospital controls [27] or have introduced compensatory strategies, e.g. excluding surgery related to current hospital admissions in controls [26]. Significant protective effects for lifetime surgery of the spine or other procedures [15, 27, 28] and for BT [27, 28, 30, 34] found in studies with age- and sex-matched controls, but with negative findings using unmatched hospital controls [35], may be explained by control selection. In contrast, some risk factors [16] may be judged to be truly significant if control groups with minimal potential bias are used.

Matching by age and sex was used in two thirds of the studies [4, 5, 9, 14, 15, 26, 27, 29–34, 36]. Matching constitutes a shortcoming in studies with protracted study pe-

riods when either population [31] or hospital [14] controls are sampled at the end of the study. The need to identify individuals of the same age at the end of the study requires sampling later birth cohorts who underwent medical procedures at a later calendar time when surgical practices or policy may have changed (see bidirectional arrows in fig. 4c). Bias in such cases is contrary to the policy time trend for the relevant age and sex group. For instance, protective effects from tonsillectomy, a procedure undertaken at a lower mean age in population controls, may be explained by increasing tonsillectomy trends in schoolchildren in the 1930s, as seen at the UK [46]. The death of patients predating the sampling of unmatched control at the end of a 30-year study period may in part underlie some of the associations seen for specific types of surgery in Australia, e.g. cholecystectomy or retina surgery, particularly if there was a decreasing trend for specific types of surgery between 1970 and 2000 [31].

Potential Biases due to Exposure Ascertainment. Medical procedures constitute exposures that may be repeated. In consequence, the individually accumulated exposure to prions can be a complex function of the number and type of medical procedures and the duration of the lifetime interval at risk of exposure. The measurement of exposure frequency is problematic when controls are not matched by age if differences in proportions of persons exposed are due to different average lifetimes at risk of exposure in cases and controls [39]. Even in register-based studies, such differential bias is likely to be modest and would not explain large ORs, but would lead to an underestimation of risk because of the longer duration of the lifetime at risk of exposure in controls sampled at the end of a study (see exposure events differential between the controls in fig. 4c). Such bias is controlled by creating an index time point close to the longitudinally sampled time units [9, 10]. The correction is also implicitly done in studies matching for age, and by stratification in unmatched designs, as was done in the CJD surveillance-based Japanese and Italian studies [16, 35]. Bias inherent in unmatched designs, with population controls identified after the clinical onset in the cases, has been circumvented in two ways: (1) using a genuine longitudinal year-by-year sampling supported by annual national population registries [9, 10] or (2) conducting a complementary subanalysis of almost simultaneously identified cases, for 2001–2005, and controls, for 2002–2003, in the UK [34]. Poor record keeping makes studies vulnerable to bias and low statistical power.

Recall is a potential source of bias present in the majority of the reviewed studies for multiple reasons: (1) re-

sponses to questions rely on the memory of the informant; (2) the choice or availability of proxy informants varied between studies [13, 14, 31, 32]; (3) since recall accuracy may be influenced by the time elapsed between exposure and recall [47], a further factor may be obtaining information from controls at the end of long study periods [31], and (4) biased responses may be derived from cases as data is obtained after the diagnosis of CJD and respondents may be aware of the hypotheses being tested.

Control of Confounding. SP are frequently associated with other procedures, e.g. transluminal endoscopies, biopsies or BT, and these potential confounders have been controlled for in only 2 studies [9, 16]. The findings from Eurosurveillance suggest that the risk from endoscopies is low [9]. In a recent Italian study all the evidence of risk due to surgery was removed by controlling for the effect of BT, suggesting that BT explained the apparent risk excess of concomitant surgery [16]. Public health recommendations for blood or plasma products and invasive procedures should consider both confounded and independent risk effects.

Biological Covariates Determining Effect Measures: Latency and Age. A protracted latency in CJD can be assumed from clinical observations on iCJD and experimental studies [21, 23, 24, 48]. Latency analysis is essential since lifetime frequency of surgery was high in cases (89%) and in controls (79%) [34] and unexposed individuals are rare. Latency analysis has provided positive results for surgery and BT at >10-year lag in 2 studies [9, 16], 1 of which was register-based [9], but not in the 2 UK studies [4, 17], and at <10-year lag for surgery in 2 studies [9, 29]. Currently two thirds of surgical interventions in Swedish hospitals, and probably in other Western countries, occur over the age of 50 years [9]. Most of these procedures would not be relevant to CJD causation at >20-year latency, particularly if the risk decreases with a more advanced age at surgery as suggested by Eurosurveillance, and due to <20-year survival [9]. The fact that 30–50% of SP or BT exposures occur at a more advanced age and are not likely to be relevant to the cause of CJD will have an impact on risk assessment when neglecting latency, i.e. diluting the effect from procedures undergone earlier in life, which may have a higher inherent risk. The majority of studies do not include a latency analysis at >10-year lag, and many use hospital controls or controls sampled at the end of the study period. These factors, together with analysis of SP carried out more frequently with time, may lead to an underestimation of risk for SP and BT.

Age appears to be a biological risk modifier for human prion diseases since the incidence of sCJD or vCJD varies with age. The effect of age at onset is taken into account in many studies by matching or in analysis. However, age may have a complex effect in case-control studies. For example, the risk of sCJD increases with a lower age at surgery [9], and the risk of iCJD associated with human pituitary growth hormone treatment is highest in the 8- to 10-year age group [21], suggesting that susceptibility to CJD is influenced by age at exposure. An age-related susceptibility function was found to be necessary to reproduce the characteristics of the age distribution of vCJD cases in the UK [49]. Furthermore, age at exposure to surgery and age at onset of sCJD were found to be directly associated [9]. In consequence, three age-related effects need to be independently considered in CJD studies: (1) age at exposure to medical procedures, (2) age at clinical onset and (3) age at the time of exposure assessment, which determines the length of the studied lifetime interval. All three factors should be evaluated as possible sources of bias in the quality assessment of studies which are used for supporting recommendations for risk prevention.

Conclusion

This review reveals a number of potential methodological pitfalls in case-control studies on CJD. Susceptibility to bias may be due to (a) the use of hospital controls and sampling controls close to or at the end of long case incidence periods, (b) exposure assessment in different lifetime periods for cases and controls or disregarding time-at-risk effects and (c) potential confounding by concurrent procedures, particularly surgery and intra-operative BT. One way to synthesize the findings in these studies, which are summarized in figure 3, is to focus on specific procedures or analyze groups of associations. The interpretation of the biological significance of statistical association patterns requires consideration of experimental and social research, e.g. evidence from laboratory transmission studies and the temporal evolution of surgical technology. These issues are mentioned in some studies [9, 10, 16] and are outside of the scope of this review.

In the context of the caveats described above, which would preclude conducting any metaanalysis prior to a quality assessment of specific studies, the conclusions below may be suggested after a review of the case-control studies in CJD.

Despite compelling evidence of case-to-case transmission of vCJD by BT [3, 50], case-control studies do not disclose an excess risk of vCJD from previous BT (or surgery and dentistry) [4, 5]. This underlines the limitations in the case-control methodology in identifying rare causal exposures and indicates that negative findings in case-control studies in other forms of CJD cannot exclude the possibility of infrequent transmission events.

Case-control data on medical procedures in iCJD and gCJD are scarce [16, 30]. One study quantifying the association of human dura mater grafts with CJD confirms a causal relationship, which is supported by clear clinical evidence [30].

In sCJD there are several positive associations with decreasing biological plausibility:

- (1) Although there is unconfirmed evidence of stress as a clinical trigger for sCJD [29], an increased frequency of surgery during the prodromal phase or early clinical course in sCJD is likely to be a consequence of the clinical features of the disease. These were quantified in 1 small study [29] and suggested in 2 other studies in which evidence of the clinical indications for surgery were provided [33, 35], e.g. CNS neoplasms or cataracts presenting with clinical features that mimicked sCJD. These findings are consistent with experience from clinical observations in sCJD and sCJD surveillance programs.
- (2) Positive associations for SP and BT, with the strongest evidence of an association based on latency analysis at >10- or >20-year lag [9, 10, 16, 34], are consistent with the protracted incubation periods in human prion disease, but may involve organs or tissues that are not known to be infectious in sCJD [9, 10]. Although case-control studies must be interpreted with caution because of the potential for systematic sources of error [16], the positive findings in relation to SP and BT may indicate a true risk for sCJD, although there may be confounding of SP by BT as mentioned above. Positive associations obtained from studies with less rigorous methodologies [31] should be interpreted with caution.
- (3) Positive associations with specific procedures at a shorter latency have been reported recently, e.g. retinal surgery with about a mean 10-year lag or coronary surgery in the decade preceding sCJD onset [9, 10]. The interpretation of these findings requires an assessment of specific, speculative hypotheses. Possibilities include the direct spread of prions to the retina, or the confounding by risk factors shared by coronary disease and sCJD [9, 10], as an issue of debate in coronary bypass surgery and Alzheimer's disease [51, 52].

- (4) Inverse associations, particularly if obtained from studies with the above-mentioned potential sources of systematic error, are most likely attributable to bias [27, 28].
- (5) The negative findings for neurosurgery may be explained by limited or inappropriate reference groups (exposed to other surgery) or by the use of hospital controls [28, 32], or perhaps because the risk of transmission through potentially contaminated neurosurgical instruments has been reduced by modern decontamination techniques.

There is limited evidence from case-control studies of an excess risk for the development of sCJD from BT and from general surgery after long latencies, and of an excess of surgery close to clinical onset. There is no epidemiological evidence of a risk from invasive dental treatments and endoscopic procedures. This evidence has to be judged in relation to other evidence, e.g. negative look-back studies of BT in sCJD [37]. This review suggests that there is a need for further research and an evidence-based review of policies for the prevention of sCJD in medical settings, for example in EU countries.

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References

- 1 Prusiner SB: The prion diseases. *Brain Pathol* 1998;8:499–513.
- 2 Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, et al: Transmissions to mice indicate that ‘new variant’ CJD is caused by the BSE agent. *Nature* 1997;389:498–501.
- 3 Hewitt PE, Llewelyn CA, Mackenzie J, Will RG: Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. *Vox Sang* 2006;91:221–230.
- 4 Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Leitch M, Cooper S, et al: Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Ann Neurol* 2006;59:111–120.
- 5 Everington D, Smith AJ, Ward HJ, Letters S, Will RG, Bagg J: Dental treatment and risk of variant CJD – a case control study. *Br Dent J* 2007;202:E19, discussion 470–471.
- 6 Riggs JE, Moudgil SS, Hobbs GR: Creutzfeldt-Jakob disease and blood transfusions: a meta-analysis of case-control studies. *Mil Med* 2001;166:1057–1058.
- 7 Barash JA, Johnson BT, Gregorio DI: Is surgery a risk factor for Creutzfeldt-Jakob disease? Outcome variation by control choice and exposure assessments. *Infect Control Hosp Epidemiol* 2008;29:212–218.
- 8 de Pedro-Cuesta J, Bleda J, Rabano A, Cruz M, Laursen H, Molbak K, et al: Classification of surgical procedures for epidemiologic assessment of sporadic Creutzfeldt-Jakob disease transmission by surgery. *Eur J Epidemiol* 2006;21:595–604.
- 9 Mahillo-Fernandez I, de Pedro-Cuesta J, Bleda J, Cruz M, Molbak K, Laursen H, et al: Surgery and risk of sporadic Creutzfeldt-Jakob disease in Denmark and Sweden: registry-based case-control studies. *Neuroepidemiology* 2008;31:229–240.
- 10 de Pedro-Cuesta J, Mahillo-Fernandez I, Rabano A, Calero M, Cruz M, Siden A, et al: Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: results from a risk-based assessment of surgical interventions. *J Neurol Neurosurg Psychiatry* 2011;82:204–212.
- 11 Ward HJ, Knight RS: Surgery and risk of sporadic Creutzfeldt-Jakob disease. *Neuroepidemiology* 2008;31:241–242.
- 12 Ruiz-Tovar M, de Pedro-Cuesta J, Smith A, Alonso C, Calero M, Pocchiari M, et al: Review of guidelines for prevention of Creutzfeldt-Jakob disease transmission in medical settings in EU member states and Norway. Stockholm, ECDC Technical Report, 2011. http://www.ecdc.europa.eu/en/publications/Publications/1106_TER_Review_of_guidelines_for_prevention_of%20CJD.pdf (cited 2011 June 21).

- 13 Kondo K, Kuroiwa Y: A case control study of Creutzfeldt-Jakob disease: association with physical injuries. *Ann Neurol* 1982;11:377–381.
- 14 Davanipour Z, Alter M, Sobel E, Asher D, Gajdusek DC: Creutzfeldt-Jakob disease: possible medical risk factors. *Neurology* 1985;35:1483–1486.
- 15 Harries-Jones R, Knight RS, Will RG, Cousens SN, Smith PG, Matthews WB: Creutzfeldt-Jakob disease in England and Wales, 1980–1984: a case-control study of potential risk factors. *J Neurol Neurosurg Psychiatry* 1988;51:1113–1119.
- 16 Puopolo M, Ladogana A, Vetrugno V, Pocchiari M: Transmission of sporadic Creutzfeldt-Jakob disease by blood transfusion: risk factor or possible biases. *Transfusion* 2011;51:1556–1566.
- 17 Molesworth AM, Mackenzie J, Everington D, Knight RS, Will RG: Sporadic Creutzfeldt-Jakob disease and risk of blood transfusion in the United Kingdom. *Transfusion* 2011;51:1872–1873.
- 18 Abrams JY, Schonberger LB, Belay ED, Maddox RA, Leschek EW, Mills JL, et al: Lower risk of Creutzfeldt-Jakob disease in pituitary growth hormone recipients initiating treatment after 1977. *J Clin Endocrinol Metab* 2011;96:E1666–E1669.
- 19 Linsell L, Cousens SN, Smith PG, Knight RS, Zeidler M, Stewart G, et al: A case-control study of sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of clustering. *Neurology* 2004;63:2077–2083.
- 20 Rabano A, de Pedro-Cuesta J, Molbak K, Siden A, Calero M, Laursen H: Tissue classification for the epidemiological assessment of surgical transmission of sporadic Creutzfeldt-Jakob disease. A proposal on hypothetical risk levels. *BMC Public Health* 2005;5:9.
- 21 Swerdlow AJ, Higgins CD, Adlard P, Jones ME, Preece MA: Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003;61:783–791.
- 22 Wientjens DP, Rikken B, Wit JM, Hofman A, Stricker BH: A nationwide cohort study on Creutzfeldt-Jakob disease among human growth hormone recipients. *Neuroepidemiology* 2000;19:201–205.
- 23 Buchanan CR, Preece MA, Milner RD: Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. *BMJ* 1991;302:824–828.
- 24 Mills JL, Fradkin JE, Schonberger LB, Gunn W, Thomson RA, Piper J, et al: Status report on the US human growth hormone recipient follow-up study. *Horm Res* 1990;33:116–119.
- 25 Nakamura Y, Aso E, Yanagawa H: Relative risk of Creutzfeldt-Jakob disease with cadaveric dura transplantation in Japan. *Neurology* 1999;53:218–220.
- 26 Esmonde TF, Will RG, Slattery JM, Knight RS, Harries-Jones R, de Silva R, et al: Creutzfeldt-Jakob disease and blood transfusion. *Lancet* 1993;341:205–207.
- 27 van Duijn CM, Delasnerie-Laupretre N, Masullo C, Zerr I, de Silva R, Wientjens DP, et al: Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993–95. European Union (EU) Collaborative Study Group of Creutzfeldt-Jakob disease (CJD). *Lancet* 1998;351:1081–1085.
- 28 Zerr I, Brandel JP, Masullo C, Wientjens DP, de Silva R, Zeidler M, et al: European surveillance on Creutzfeldt-Jakob disease: a case-control study for medical risk factors. *J Clin Epidemiol* 2000;53:747–754.
- 29 Laske C, Gefeller O, Pfahlerberg A, Zerr I, Schroter A, Poser S: The effect of stress on the onset and progression of Creutzfeldt-Jakob disease: results of a German pilot case-control study. *Eur J Epidemiol* 1999;15:631–635.
- 30 Nakamura Y, Oki I, Tanihara S, Ojima T, Yanagawa H, Kitamoto T, et al: A case-control study of Creutzfeldt-Jakob disease in Japan: transplantation of cadaveric dura mater was a risk factor. *J Epidemiol* 2000;10:399–402.
- 31 Collins S, Law MG, Fletcher A, Boyd A, Kaldor J, Masters CL: Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:693–697.
- 32 Ward HJ, Everington D, Croes EA, Alperovitch A, Delasnerie-Laupretre N, Zerr I, et al: Sporadic Creutzfeldt-Jakob disease and surgery: a case-control study using community controls. *Neurology* 2002;59:543–548.
- 33 S-Juan P, Ward HJ, de Silva R, Knight RS, Will RG: Ophthalmic surgery and Creutzfeldt-Jakob disease. *Br J Ophthalmol* 2004;88:446–449.
- 34 Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Gillies M, Murray K, et al: Risk factors for sporadic Creutzfeldt-Jakob disease. *Ann Neurol* 2008;63:347–354.
- 35 Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T, et al: Medical procedures and risk for sporadic Creutzfeldt-Jakob disease, Japan, 1999–2008. *Emerg Infect Dis* 2009;15:265–271.
- 36 Ruegger J, Stoek K, Amsler L, Blaettler T, Zwahlen M, Aguzzi A, et al: A case-control study of sporadic Creutzfeldt-Jakob disease in Switzerland: analysis of potential risk factors with regard to an increased CJD incidence in the years 2001–2004. *BMC Public Health* 2009;9:18.
- 37 Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari E, et al: Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. *Transfusion* 2009;49:977–984.
- 38 Zaman SM, Hill FG, Palmer B, Millar CM, Bone A, Molesworth AM, et al: The risk of variant Creutzfeldt-Jakob disease among UK patients with bleeding disorders, known to have received potentially contaminated plasma products. *Haemophilia* 2011;17:931–937.
- 39 Rothman KJ, Greenland S, Lash TL: Case-control studies; in *Modern Epidemiology*, ed 3. Philadelphia, Lippincott Williams & Wilkins, 2008, pp 111–127.
- 40 Wacholder S: The case-control study as data missing by design: estimating risk differences. *Epidemiology* 1996;7:144–150.
- 41 Weightman A, Ellis S, Cullum A, Sander L, Turley R: Grading evidence and recommendations for public health interventions: developing and piloting a framework. Health Development Agency 2005, March 31. <http://www.nice.org.uk/download.aspx?o=503421> (cited 2010 May 11).
- 42 Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al: Going from evidence to recommendations. *BMJ* 2008;336:1049–1051.
- 43 Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, et al: Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. *Neurology* 2005;64:1586–1591.
- 44 Josephs KA, Ahlskog JE, Parisi JE, Boeve BF, Crum BA, Giannini C, et al: Rapidly progressive neurodegenerative dementias. *Arch Neurol* 2009;66:201–207.
- 45 Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I: Rapidly progressive Alzheimer disease. *Arch Neurol* 2011;68:1124–1130.
- 46 Glover JA: The incidence of tonsillectomy in school children. 1938. *Int J Epidemiol* 2008;37:9–19.
- 47 Klemetti A, Saxen L: Prospective versus retrospective approach in the search for environmental causes of malformations. *Am J Public Health Nations Health* 1967;57:2071–2075.
- 48 Gravenor MB, Stallard N, Curnow R, McLean AR: Repeated challenge with prion disease: the risk of infection and impact on incubation period. *Proc Natl Acad Sci USA* 2003;100:10960–10965.
- 49 Boelle PY, Cesbron JY, Valleron AJ: Epidemiological evidence of higher susceptibility to vCJD in the young. *BMC Infect Dis* 2004;4:26.
- 50 Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens SN, Mackenzie J, et al: Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004;363:417–421.
- 51 Beeri MS, Rapp M, Silverman JM, Schmeidler J, Grossman HT, Fallon JT, et al: Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. *Neurology* 2006;66:1399–1404.
- 52 Lee TA, Wolozin B, Weiss KB, Bednar MM: Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. *J Alzheimers Dis* 2005;7:319–324.

Erratum

In the article by de Pedro Cuesta et al., entitled ‘Sensitivity to biases of case-control studies on medical procedures, particularly surgery and blood transfusion, and risk of Creutzfeldt-Jakob disease’ [Neuroepidemiology 2012;39:1–18, DOI: 10.1159/000339318], the authors noticed to their dismay that line 4 of the Introduction contains an error which could very easily mislead the reader.

As published, the phrase in question reads ‘CJD exists in three forms: sporadic (sCJD), which is acquired, either variant (vCJD) or iatrogenic (iCJD) CJD, and cases caused by mutations in the gene-encoding PrP^C, here denoted for purposes of simplicity as genetic CJD (gCJD) [1]’. The words ‘which is’ are clearly erroneous and should be deleted. The sentence correctly reads ‘CJD exists in three forms: sporadic (sCJD), acquired, either variant (vCJD) or iatrogenic (iCJD) CJD, and cases caused by mutations in the gene-encoding PrP^C, here denoted for purposes of simplicity as genetic CJD (gCJD) [1]’.